IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Robert Eugene Handfield Jr. *et. al.*	Examiner: Oh, Taylor V
APPLICATION NO.: 10/714,735	Group Art Unit: 1625
FILING DATE: November 17, 2003	
TITLE: IMPROVED PROCESS FOR THE PREPARTION OF 1,3-SUBSTITUTED INDENES	

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

DECLARATION OF ROBERT E. HANDFIELD Jr. AND TIMOTHY J. WATSON UNDER 37 C.F.R. §1.132

We, Robert E. Handfield Jr. and Timothy J. Watson, declare as follows:

1. We are Pfizer scientists working at Pfizer Global Research and Development in Groton, Connecticut under the official titles of Research Scientist and Associate Research Fellow, respectively.
2. We have extensive training in the science of chemistry, and specifically in organic and process chemistry, and the research and development of pharmaceutically useful crystalline forms for application in clinical medicine. In particular, we have significant experience in the field of crystallization development of small molecules. I, Robert E. Handfield Jr., hold a B.S. degree in biology and have 21 years of experience in the field; and I, Timothy J. Watson, hold a Ph.D. in organic chemistry and have 13 years of experience in the field. Collectively, we have nearly 34 years of experience in the field. We are authors or co-authors of numerous research publications in the field, and are inventors or co-inventors of patents directed to various crystalline forms of novel pharmaceutical substances.
3. We are co-inventors of the above named patent application which is directed to an improved process for the preparation of 1,3-substituted indenes. We understand the technical issues surrounding such process and herein further attest to the following:
4. We have compared the process for preparing 1,3-substituted indenes of the claimed process with the process of the prior art, and have found that the claimed process of the present invention produces superior and unexpected results when compared with the prior art.

5. As well known in the art, processes most suitable for industrial manufacture maximize stability, purity, solubility, or yield, or a combination thereof, or some other physiochemical property of intermediates such as, as in this case, 1,3-substituted indenes. Moreover, preferred processes yield reaction mixtures or products in a solid, rather than gelatinous state and generate negligible amounts of a surfactant; preferably the reaction mixtures or products are free from any detectable amounts of a surfactant. The claimed process contains many of these desirable attributes and results in a superior process for preparing 1,3-substituted indenes.
6. The claimed process describes the addition of a distillation step to remove inert solvent, in this case, tetrahydrofuran (THF), and the addition to the reaction mixture of ammonium hydroxide. The combination of adding ammonium hydroxide and the distillation step controls solubility of the desired product 1,3-substituted indenes and also produces 1,3-substituted indenes in a solid, rather than gelatinous state. The combination of adding ammonium hydroxide and the distillation step to remove THF from the ethylene glycol cyclization step forming the indene products offers two advantages over the prior art:

   (a) First, removal of solvent by distillation eliminated the formation of undesirable traces of 1, 4-dibutanol in the reaction mixture, which interfered with the reaction and adversely affected yield; and

   (b) Second, removal of solvent by distillation minimized foaming believed to result from in situ formation of a surfactant, thereby producing 1,3-substituted indenes in a more preferable solid state, rather than in a undesirable gelatinous state.

   Moreover, addition of ammonium hydroxide quenches sulfuric acid to cause formation of ammonium sulfate which helps to minimize the amount of water required for isolation of 1,3-substituded indenes. Consequently, the combination of adding ammonium hydroxide and the distillation step improved the process of preparing 1,3-substituted indenes by controlling purity and stability, and significantly improving yield. The data table below illustrates representative data showing the percent purity of 1,3-substituted indenes, their stability over a two year period, and comparing the percent yield as a result of this combination of steps.

1,3-Substituted Indene (Representative Data)				
Notebook Ref.	%Yield BEFORE NH_4OH and distillation step	%Yield **AFTER**-NH_4OH and distillation step	% Purity	Stability (%Impurity Increase over 2-year period)
41385-94-6	54.50%	91.60%	80-99%	Only 1-2% Impurity (2-year period)
41385-96-8				
41385-97-11				
41385-99-10				

7. The improved physiochemical properties of 1,3-substituted indenes as measured by stability, purity, and improved yield derived from use of ammonium hydroxide and a distillation step makes this method of preparing 1,3-substituted indenes most desirable and suitable for industrial manufacture and commercial use.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 03, 2007 /Robert E. Handfield Jr./
Robert E. Handfield Jr.

Date: May 03, 2007 /Timothy J. Watson/
Timothy J. Watson, Ph.D.